Increasing Complexity at All Costs – But Why?

Traditional in vitro models have relied on single-cell-type systems cultured under submerged conditions in standard multi-well plates. These reductionist models offered robustness, reproducibility, and experimental control.

In recent years, however, there has been a strong move toward increasingly complex systems, including multi-cell-type co-cultures and three-dimensional models such as lung cells grown at the air–liquid interface (ALI). These advanced models aim to better mimic physiological conditions and are often assumed to be more predictive of in vivo responses.

Yet greater complexity does not automatically translate into greater validity.

When multiple cell types are combined, cellular behavior can change substantially. Gene expression, signaling pathways, and functional responses are shaped by cell–cell interactions and culture conditions such as ALI. Therefore, it is essential to characterize not only individual cell types, but also the dynamic properties of the entire system. Increased complexity can also introduce variability and reduce mechanistic clarity.

Furthermore, complex in vitro models must be systematically compared with both human in vivo tissues and the animal models they seek to replace. Similarity cannot be assumed—it must be demonstrated.

The objective of model development should not be maximal complexity, but optimal predictive performance. In vitro systems should be as complex as necessary to capture relevant physiological mechanisms, yet as simple as possible to remain robust, reproducible, and practical.

Complexity is a tool—not a goal in itself.